CLAIMS

1. An oral multiparticulate pharmaceutical form comprising pellets having a size in the range from 50 to 2500 µm, which are substantially composed of

a) an inner matrix layer comprising an active substance which is a peptide or a protein, including derivatives or conjugates thereof, and is embedded in a matrix of a polymer having a mucoadhesive effect, where the matrix may optionally comprise further pharmaceutically usual excipients,

b) an outer film coating consisting essentially of an anionic polymer or copolymer which may optionally be formulated with pharmaceutically usual excipients, especially plasticizers,

characterized in that

the multiparticulate pharmaceutical form is formulated so that the contained pellets are released in the pH range of the stomach, the outer coating is adjusted through the choice of the anionic polymer or copolymer or its formulation with excipients and its layer thickness such that the coating dissolves in pH ranges from 4.0 to 8.0 in the intestine within 15 to 60 min, so that the active substance-containing, mucoadhesive matrix layer is exposed, and can bind to the intestinal mucosa and release the active substance there, where the polymer having a mucoadhesive effect is chosen so that it exhibits a mucoadhesive effect of η_b = 150 to 1000 mPa·s and a water uptake of from 10 to 750% in 15 min in a range of +/- 0.5 pH units relative to the pH at which the outer coating starts to dissolve, and the active

substance content of the matrix layer is a maximum of 40% by weight of the content of polymer having a mucoadhesive effect.

2. The pharmaceutical form as claimed in claim 1, characterized in that the outer film coating is cellulose glycolate (Duodcell®), cellulose acetate phthalate (CAP, Cellulosi acetas, PhEur, cellulose acetate phthalates, NF, Aquaterie®), cellulose acetate succinate (CAS), cellulose acetate trimeliate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP, HP50, HP55), hydroxypropylmethylcellulose acetate succinate (HPMCAS-LF, -MF, -HF), polyvinyl acetate phthalate (PVAP, Sureteric®), vinyl acetate-vinylpyrrolidone copolymer (PVAc, Kollidon® VA64), vinyl acetate:crotonic acid 9:1 copolymer (VAC:CRA, Kollicoat® VAC) and/or shellack.

3. The pharmaceutical form as claimed in claim 1, characterized in that the outer film coating consists of a (meth)acrylate copolymer having a content of monomers having anionic groups of from 5 to 60% by weight.

4. The pharmaceutical form as claimed in one or more of claims 1 to 3, characterized in that the layer thickness of the outer coating is in the range from 20 to 200 µm.

5. The pharmaceutical form as claimed in one or more of claims 1 to 4, characterized in that the inner matrix comprises a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor and/or a penetration promoter.

6. The pharmaceutical form as claimed in one or more of claims 1 to 5, characterized in that the polymer having a mucoadhesive effect is a chitosan, a (meth)acrylate copolymer consisting of 20-40% by weight methyl methacrylate and 60 to 80% by weight methacrylic acid and/or a cellulose, especially Na carboxymethylcellulose, a crosslinked and/or uncrosslinked polyacrylic acid, a lectin, an Na alginate, and/or a pectin.

7. The pharmaceutical form as claimed in claim 6, characterized in that the inner matrix comprises as polymer having a mucoadhesive effect a chitosan which is employed together with an acid or a buffer system, which is located in the matrix or in or on a core onto which the matrix is applied.

8. The pharmaceutical form as claimed in claim 7, characterized in that the inner matrix layer comprises chitosan and is adjusted to pH 5.0 to 5.5 by means of an acid or a buffer system, and is combined with an outer film coating which starts to dissolve in the range from pH 6.0 to 8.0.

9. The pharmaceutical form as claimed in one or more of claims 1 to 8, characterized in that the active substance is a protein or a peptide having an average molecular weight M_w of less than 3000.

10. The pharmaceutical form as claimed in claim 9, characterized in that the active substance is abarelix, angiotensin II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, cetrorelix, cyclosporin A, desmopressin, detirelix, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, ramorelix,

secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, vasopressin.

11. The pharmaceutical form as claimed in claim 9 or 10, characterized in that the matrix layer additionally matrix comprises a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin.

12. The pharmaceutical form as claimed in one or more of claims 1 to 8, in that the active substance is a protein or peptide having an average molecular weight M_w of from 3000 to 10 000.

13. The pharmaceutical form as claimed in claim 12, characterized in that the active substance is calcitonin, corticotrophin, endorphins, epithelial growth factor, glucagon, insulin, novolin, parathyroid hormone, relaxin, pro-somatostatin or salmon secretin.

14. The pharmaceutical form as claimed in claim 12 or 13, characterized in that the matrix layer comprises a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor.

15. The pharmaceutical form as claimed in one or more of claims 1 to 9, characterized in that the active substance is a protein or peptide having an average molecular weight M_w of more than 10 000.

16. The pharmaceutical form as claimed in claim 15, characterized in that the active substance is interferon (alpha, beta, gamma), interleukins

(IL1, IL2), somatotropin, erythropoietin, tumor necrosis factor (TNF alpha, beta), relaxin, endorphin, dornase alpha, follicle stimulating hormone (FSH), human chorion gonadotropin (HCG), human growth hormone release factor (hGRF), luteinizing hormone (LH) or epidermal growth factor.

17. The pharmaceutical form as claimed in claim 15 or 16, characterized in that the matrix layer comprises a C_6- to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives and/or a lipid and/or a phospholipid and/or a lipid-soluble vitamin and/or a protease inhibitor and/or a penetration promoter.

18. The pharmaceutical form as claimed in one or more of claims 1 to 17, characterized in that a separating layer is applied between the active substance-containing matrix layer and the outer film coating layer.

19. A process for producing a multiparticulate pharmaceutical form as claimed in one or more of claims 1 to 18, by

a) producing an inner matrix layer comprising an active substance, which is a peptide or a protein, and a polymer having a mucoadhesive effect and, where appropriate, further pharmaceutically usual excipients by means of spray application onto a core or by rotagglomeration, precipitation or spray processes without a core, and subsequently

b) applying an outer film coating consisting essentially of an anionic polymer or copolymer, which may optionally be formulated with pharmaceutically usual excipients, especially

plasticizers, by means of spray application so that active substance-containing, enveloped pellets are obtained, and

c) processing the resulting pellets by means of pharmaceutically usual excipients in a manner known per se to a multiparticulate pharmaceutical form, in particular to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable powders, which are formulated so that the contained pellets are released in the pH range of the stomach.

20. The pharmaceutical form as claimed in one or more of claims 1 to 18, characterized in that the active substance is embedded in a lipophilic matrix which has a melting point above 37°C, and the active substance-containing lipophilic matrix is embedded in the matrix composed of the polymer having a mucoadhesive effect.

21. The pharmaceutical form as claimed in claim 20, characterized in that the active substance and the substance or substances forming the lipophilic matrix differ in their solubility in water according to DAB 10 and not more than +/- 50%, and/or differ in their partition coefficient according to annex V to directive 67/548/EEC, A.8 by not more than +/- 60%, and/or differ in their HLB measured by the method of Marszall not more +/- 80%.

22. The pharmaceutical form as claimed in claim 20 or 21, characterized in that an active substance which has a solubility in water according to DAB 10 of at least 30 parts by volume of water for one part by weight of active substance is present.

23. The pharmaceutical form as claimed in claim 22, characterized in that the active substance is

selected from the group of peptide antibiotics, immunosuppressants, LHRH antagonists, immunomodulators.

24. The pharmaceutical form as claimed in claim 22 or 23, characterized in that the active substance is abarelix, angiotensin II, anidulafungin, antide, argipressin, azaline and azaline B, bombesin antagonist, bradykinin, buserelin, calcitonin, cetrorelix, cyclosporin, cyclosporin A, desmopressin, detirelix, erythropoietin, encephalins (Leu-, Met-) ganirelix, gonadorelin, goserelin, growth hormone secretagogue, insulin, interferon (alpha, beta, gamma), interleukins (IL1, IL2), micafungin, nafarelin, leuprolide, leuprorelin, octreotide, orntide, oxytocin, parathyroid hormone, ramorelix, secretin, somatotropin, terlipressin, tetracosactide, teverelix, triptorelin, thyroliberin, thyrotropin, tumor necrosis factor (TNF alpha, beta) or vasopressin.

25. The pharmaceutical form as claimed in one or more of claims 20 to 24, characterized in that the substance or substances forming the lipophilic matrix, and the polymer having a mucoadhesive effect either have the same ionic property or, in the event of opposed ionic properties, the polymer having a mucoadhesive effect is present in at least 50% neutralized form.

26. The pharmaceutical form as claimed in one or more of claims 20 to 25, characterized in that the lipophilic matrix consists of 80 to 100% by weight of a substance having an HLB of from 0 to 15 or of a mixture of substances having an average HLB of from 0 to 15, and may comprise from 0 to 20% by weight of pharmaceutically usual excipients, especially stabilizers, thickeners or adsorbents.

27. The pharmaceutical form as claimed in one or more of claims 20 to 26 characterized in that the substance or the substances forming the lipophilic matrix belong to the group of oils, fats, mono-, di- or triglycerides, fatty acids, fatty alcohols, especially C_6 to C_{20}-fatty acid and/or a C_6- to C_{20}-alcohol including their salts, ether, ester or amide derivatives, phospholipids, lecithins, emulsifiers, lipoids, lipid-soluble vitamins or surfactants.

28. The pharmaceutical form as claimed in one or more of claims 20 to 26, characterized in that the lipophilic matrix comprises one of the following lipid preparations: (Imwitor 308) glyceryl monocaprylates having a monoester content of > 80%, (Imwitor 312) glyceryl monolaurates having a monoester content of > 90%, (Imwitor 491) glycerol monostearates (C_{16} + C_{18}) having a monoester content of > 90%, (Imwitor 900 P) glycerol monostearate having a monoester content of 40-55% and a C_{18} content of 40-60%, (Imwitor 900 K) glycerol monostearate, having a monoester content of 40-55% and a C_{18} content of 60-80%, (Imwitor 742) medium chain-length C_8 and C_{10} glycerides having a monoester content of 45-55%, (Imwitor 928) partial glycerides of saturated vegetable C_{10}-C_{18} fatty acids having a main content of C_{12}, and having a monoester content of 34-36%, C_8 and C_{10} glycerides, Na caprylate or Na capriate.

29. The pharmaceutical form as claimed in one or more of claims 20 to 28, characterized in that the active substance is at least 10% soluble in the lipophilic matrix.

30. The pharmaceutical form as claimed in one or more of claims 20 to 29, characterized in that the

content of active substance-containing lipophilic matrix in the inner matrix layer a) is from 5 to 50% by weight.

31. A process for producing a multiparticulate pharmaceutical form as claimed in one or more of claims 20 to 30, with the steps

a) production of the active substance-containing lipophilic matrix by suspending and/or dissolving the active substance with the substance(s) which form the lipophilic matrix and, where appropriate, further pharmaceutically usual excipients by vigorously mixing or melting the ingredients,

b) production of pre-pellets (pellet cores) by spray application of the mucoadhesive polymer mixed with the active substance-containing lipophilic matrix onto a core or by rotagglomeration, precipitation or spray processes without a core,

c) production of pellets by spray application of a coating of the anionic polymer or copolymer, which may optionally comprise admixtures of pharmaceutically usual excipients, especially plasticizers and release agents, from a dispersion or organic solution onto the pre-pellets from step b),

d) production of a multiparticulate pharmaceutical form by filling or incorporating the pellets from step c) in a manner known per se, where appropriate with use of pharmaceutically usual excipients, in particular by processing to pellet-containing tablets, minitablets, capsules, sachets or reconstitutable powders.

32. The process for producing a multiparticulate pharmaceutical form as claimed in claim 31, characterized in that steps a) and b) are carried

out as follows

a) production of the inner matrix layer by preparing an emulsion, dispersion or solution of the active substance with the substance(s) for the lipophilic matrix, and where appropriate further pharmaceutically usual excipients by vigorously mixing the ingredients in water and producing an oil-in-water preparation having an average particle size of not more than 60 µm,

b) production of pre-pellets by spray application of the oil-in-water preparation from step a) onto the mucoadhesive polymer which may optionally comprise admixtures of further pharmaceutically usual excipients, where the ingredients are in the form of a micronized powder, by rotagglomeration, extrusion or granulation.